

## Cost-Effectiveness Analysis for the Treatment of Chronic Kidney Disease with Low-Protein Diet

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### **ABSTRACT:**

**Background:** Several clinical studies have shown that a low protein diet in patients with Chronic Kidney Disease (CKD), delays and prevents the natural progression of the end stage renal disease (ESRD) and the necessary treatment of renal dialysis. Studies to investigate the effects of the low protein diets in preventing severe kidney failure are few for Italy. The aim of this study is to estimate the cost-effectiveness of a low protein diet treatment compared with no dietary treatment in patients with CKD 4-5 after 2, 3, 5 and 10 years.

**Methods:** A Markov model simulating was developed to estimate costs and QALYs associated with low protein treatment and no treatment for patients with CKD 4-5. The prevalence of patients with CKD 4-5 refers to a population aged  $\geq 40$  years old was 0.3% estimated by a study of Gambaro et al. on the 2010. The transition probability was estimated on data from seven studies identified by a Cochrane review to determine the efficacy of low protein diets in delaying the need to start maintenance dialysis. The Quality Adjusted Life Years (QALYs) scores used were estimated with the Time Trade Off by a study of Gorodetskaya et al. in 2005. The costs of dialysis have been estimated by a study of Censis (2009) and amounted to approximately €34,071.7 per patient per year. The costs of a low-protein diet refer to contributions of €1,440 per patient per year made by Lazio Region for patients that use a low-protein diet.

**Main Results / Conclusion:** The treatment with a low-protein diet is more effective in terms of QALYs: the difference is always in favour of dietary treatment from a 0.09 after the first two years, 0.17 after three years, 0.37 after five years and up to a differential of 1 year after the first 10 years of treatment. In terms of cost-effectiveness, the dietary treatment is always

dominant in all the intervals considered. The dominance is due to the fact that the treatment is more effective in terms of QALYs and at the same time is less expensive. The results of these simulations indicate that the treatment of patients with CKD with a low protein diet is cost effective relative to no treatment in an Italian setting.

## **INTRODUCTION:**

In recent years, chronic kidney disease has received increased attention as a leading public health problem<sup>[1]</sup>. The kidney disease burden, measured in terms of prevalence, associated economic costs, and morbidity, is substantial and increasing<sup>[2, 3]</sup>. In Italy people affected by CRF (chronic renal failure) (Glomerular Filtration Rate (GFR) < 60 ml/min per 1.73 m<sup>2</sup> of BSA<sup>[4]</sup>) represent about 6% of population<sup>[5, 6, 7]</sup>

The prevalence of individuals with chronic kidney disease (CKD) at less severe stages (1-5 DOQI) has been estimated ranging from 13% to 9% of the adult population worldwide and the number is growing<sup>[8, 9, 10]</sup>. This trend poses major challenges to health care systems<sup>[11]</sup>, reflecting the greater health care use and more comorbid conditions among elderly adults<sup>[12]</sup>.

The end-stage renal disease (ESRD) for which life can be sustained only with renal replacement therapy such as dialysis or kidney transplantation is growing and in Italy the last report from RIDT (Italian registry of dialysis and transplant) show the incidence is about 160 parts-per-million (ppm) and prevalence is about 788 ppm<sup>[13]</sup>. It means that in Italy we have about 40,000 persons in ESRD treatment.

Cardiovascular mortality in patients with ESRD is 10- to 20- fold higher than in the general population and is the leading cause of death<sup>[14, 15]</sup>. Mortality rates for patients with ESRD have shown only modest improvement over the past 2 decades<sup>[16]</sup>.

For these reasons it is necessary to reduce not only the incidence of patients in ESRD but also the complications linked to CKD Moranne<sup>[17]</sup> which some years ago showed that "Early detection of CKD and its metabolic complications is now a priority for delaying disease progression and for primary prevention of many CKD-associated chronic diseases, including cardiovascular, mineral, and bone diseases".

It is now commonly agreed that the presence of CKD identifies a higher risk state not only for the general population but overall in the elderly population, with an increased risk for multiple adverse outcomes, including kidney failure, cardiovascular disease, cognitive impairment, and death<sup>[18]</sup>.

In other words, there are many metabolic complications and it is necessary to treat them as soon as possible, in general, in class DOQI 3 or in any case when GFR is under 45 ml/min.

One of the most useful tools is the nutritional treatment Extensive studies in animals and preliminary studies in humans suggest that progression of a variety of chronic kidney diseases (CKD) may be largely due to secondary hemodynamic and metabolic factors, rather than the activity of the underlying disorder<sup>[19]</sup>.

In a variety of animal models (such as subtotal nephrectomy and diabetic nephropathy), lowering protein intake protects against the development of glomerular scarring<sup>[20]</sup>. Dietary protein restriction may also be beneficial by exerting non-haemodynamic effects<sup>[21, 22, 23]</sup>.

Multiple well-designed randomized controlled human trials have evaluated both the efficacy and safety of protein restriction in patients with progressive CKD<sup>[24]</sup>. Moderate

protein restriction (0.6 to 0.8 g/kg per day) is associated with significant benefit of protein restriction in delaying renal dialysis<sup>[25, 26, 27]</sup>. It is generally well tolerated and does not lead to malnutrition in patients with CKD providing caloric goals are met, dietary protein is of high biologic value, and metabolic acidosis is avoided<sup>[28]</sup>.

For CKD stage 3, low protein, low phosphorus diets may retard dialysis<sup>[29]</sup>. A diet providing about 0.60–0.75 g protein/kg/day, of which at least 0.35 g/kg/day is high biologic value protein, is needed to ensure a sufficient intake of the essential amino acids.

For CKD stage 4 and 5, the potential advantages of using a low-protein, low-phosphorus diet are more compelling. A low protein diet will generate less nitrogenous compounds that are potentially toxic both systemically and to the kidney itself. In addition, it generally contains less phosphorus and potassium, reductions which are usually imperative at this advanced stage of renal failure.

Not all individuals with chronic renal disease are willing and able to adhere to diets providing 0.60 g protein/kg/day or a very low protein diets. For this reason it is necessary to have a very close follow-up and nutrition counselling by a registered dietician at least 3-4 times a year.

Nutritional studies in patients with CKD suggest that protein intake can be safely lowered to 0.6 g/kg per day but an adequate caloric intake must be maintained (35 kcal/kg IBW) and at least 60 percent of the ingested protein must be of high biologic value or contain a high percentage of essential amino acids<sup>[30]</sup>.

The K/DOQI Clinical Practice Guidelines currently recommend that the energy intake for non-dialysed patients with advanced CKD (GFR  $\leq$  25 mL/minute) and for patients on maintenance dialysis should be 35 kcal/kg/day for individuals who are less than 60 years of age and 30–35 kcal/kg/day for those who are 60 years of age or older, who are usually more sedentary<sup>[31]</sup>. The same energy intakes are recommended for people with stage 3 or 4 CKD (i.e. GFR  $\geq$  60 mL/minute/1.73 m<sup>2</sup>).

Nutritional treatment is able to reduce many others metabolic complications as cardiovascular, mineral, and bone diseases reducing salt and especially phosphorous. Furthermore, the nutritional treatment, is able to ensure high caloric intake to older people to reduce or invert malnutrition that, in this class of people, is mainly due to low caloric intake rather to low protein intake<sup>[32]</sup>.

The aim of this study is to estimate the cost-effectiveness of a low protein diet treatment compared with no dietary treatment in patients with CKD 4-5 after 2, 3, 5 and 10 years.

## **METHODS:**

**Model:** The analysis was performed by developing a Markov model simulating the clinical pathway of patients with chronic kidney disease.

The model provides the possibility of being treated according to two different approaches: with a low-protein diet and with a non-low-protein diet. In our simulation, we assumed that half the prevalent patients in Italy are treated with a low-protein diet and the other half without any dietary changes.

Over the years, the clinical pathway of each patient may have one of three possible outcomes: death, end-stage kidney disease requiring dialysis and chronic kidney disease (CKD) not requiring dialysis.

The model provides that, at the end of each year considered in the analysis, deaths or patients with ESKD/on dialysis remain in the absorbing state until the end of the simulation or death (in the case of dialysed patients). Subjects who do not undergo any event remain in the chronic kidney disease state, maintaining their quality of life until the end of the follow-up period.

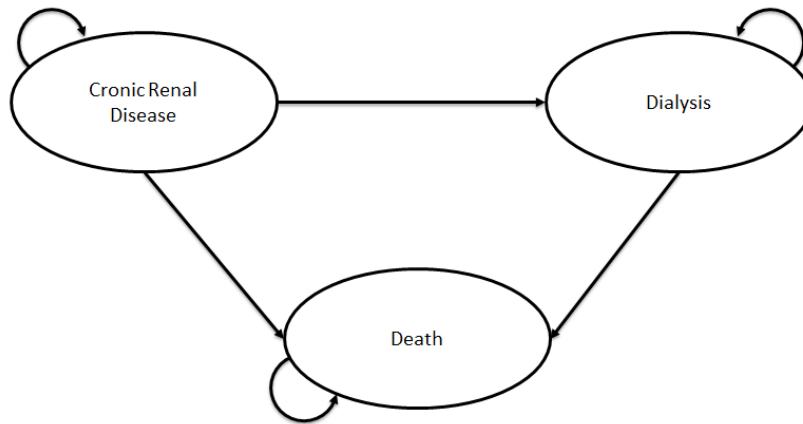


Figure 1. Markov model structure

**Epidemiological data:** In order to extrapolate the relevant national epidemiological data, a literature review was conducted using the most important international search engines (PUBMED, Cochrane Library). The study conducted by Gambaro et al. in 2010<sup>[7]</sup> estimates the prevalence of patients with CKD grade 4 aged 40 over 0.3% of the population of northeast Italy (Table I).

Table I. Demographic parameters

Demographic Data	Base Case	Min	Max	Absolute values	Source
General population of ITALY				60,626,442	ISTAT
Population over 40	55.60%			33,708,302	ISTAT
Prevalence in Italy of CKD (CKD 4) in subjects aged 40 and over	0.30%	0.15%	0.45%	101,125	Gambaro et al. 2010
Patients receiving dietary treatment	50.00%	40.00%	60.00%	50,562	ASSUMPTION

Source: Gambaro et al. 2010 [Error! Bookmark not defined.], Istat[33]

In the simulation we presumed that the number of patients treated with a low-protein diet was the same as that of patients receiving no dietary treatment. This allows a more immediate comparison between the two treatment arms in terms of the patients requiring dialysis, quality-adjusted life years (QALY) estimate and in terms of the cost of treatments during the time intervals considered.

**Model probability estimate:** The probabilities were obtained using the data presented in the study by Foque and Laville (Cochrane) in 2009<sup>[26]</sup> and pro-rated on the basis of the study conducted by De Nicola in 2011<sup>[34]</sup>. The purpose of the Cochrane review was to determine the effectiveness of a low-protein diet in delaying end-stage renal disease and the consequent

need for dialysis. To do so, 40 studies were examined, of which just 10 found suitable in terms of the data required to build a quantitative estimate of the effectiveness of low-protein diet in delaying end-stage kidney disease. Overall, the data for 2,000 patients was considered, of whom 1,000 had been treated with a low-protein diet and 1,000 with a higher protein intake.

In this analysis, a further selection was made and of the ten studies identified in the Cochrane review only seven possessed the requisites that suited our purpose. Three studies (Rosman 1989 [35], Locatelli 1991 [36], Klahr 1994 [37]) were based on a patient population with grade 3 – 5 CKD. Consequently, the number of observed patients considered in our estimates dropped to 702, of whom 351 were treated with a low-protein diet and the same number with a normal protein intake. As shown in Table II, the diets of the patients considered vary for the different studies. The analysis conducted by Mirescu et al. in 2007 [38] considered a diet with a protein intake of 0.3g/kg/day for patients receiving dietary treatment and 0.6g/kg/die for those who received no dietary treatment. In the analysis conducted by Williams et al. in 1991 [39] patients were treated with diets with protein intakes of 0.6 g/kg/day and 0.8 g/kg/day. The duration of the follow-up observation also varied from one study to another, from a minimum of 12 months for the study conducted by Junger et al. in 1987 [40] to a maximum of 24 months for the study by Di Iorio et al. in 2003 [41]. For this reason, the probabilities were standardised according to the duration of the follow-up period in the individual studies (Table II).

**Table II.** Type of diet, follow-up and patients observed per study, probability of end-stage renal disease (ESRD) or death, as total values and standardized at 1 month and 12 months for each study.

Study	Type of low-protein diet g/kg/d	Type of non-low-protein diet g/kg/d	Follow-up (months)	Patients on a low-protein diet	Patients with ESRD or death	Patients not on a low-protein diet	Patients not on a diet with ESRD or death	Probability of ESRD or death for patients on a diet	Probability of ESRD or death for patients not on a diet	ESRD/mortality rate for patients on a diet for 1 year	ESRD/mortality rate for patients not on a diet for 1 year	Probability of ESRD or death for patients on a diet for one year	Probability of ESRD or death for patients not on a diet for one year
Cianciaruso 2008	0.55	0.8	6-18	212	9	211	13	0.04	0.06	0.04	0.06	0.04	0.06
Di Iorio 2003	0.3	0.6	24	10	2	10	7	0.2	0.7	0.11	0.60	0.11	0.45
Ihle 1989	0.4	0.75	18	34	4	38	13	0.12	0.34	0.08	0.28	0.08	0.24
Jungers 1987	0.4	0.6	12	10	5	9	7	0.5	0.78	0.69	1.50	0.50	0.78
Malvy 1999	0.3	0.65	18	25	11	25	17	0.44	0.68	0.39	0.76	0.32	0.53
Mirescu 2007	0.3	0.6	15	27	1	26	7	0.04	0.27	0.03	0.25	0.03	0.22
Williams 1991	0.6	0.8	18	33	12	32	11	0.36	0.34	0.30	0.28	0.26	0.24
Mean/Total	0.4	0.7	17.5	351	44	351	75						

Source: Foque and Laville (Cochrane) 2009 [26]

Table II also shows the data from the seven studies considered with regard to the probabilities and duration of follow-up-adjusted probabilities of observing the end-stage renal disease (ESRD) event or death for patients receiving/not receiving dietary treatment. The probabilities were adjusted by calculating for each one the respective annual rate from which we then obtained the annual probabilities [42-43]. Specifically the annual mortality or ESRD rate was calculated using the following formula:

$$r = -[\ln(1 - P)] / t$$

Where P is the probability of the individual study considered and t is the amplitude of the range, expressed in years, that the probability considered refers to.

Lastly, relative probability at one year was calculated as follows:

$$p = 1 - \exp\{-rt\}$$

Where r is the annual mortality or ESRD rate and t is the amplitude of the range, expressed in years, that the probability refers to and that, in our case, will be equal to 1. Since the probabilities were standardised in relation to time, they could be grouped together in a single indicator by calculating the weighted mean for the respective arms. In the estimate, it was established that the weights associated with the individual values corresponded to the sample size of the respective studies considered. By doing so, we eliminated the potential bias produced by the different sizes of the populations analysed in the studies.

The values obtained jointly represent the risk of experiencing the end-stage renal disease event or death. However, the model used makes it possible to split this probability between the two events. It was therefore necessary to estimate the weight of the two events within this probability. The respective weights of the two events on combined probability were estimated using the data of the study conducted by De Nicola et al. [34] in 2011 that estimated the probability of observing the end-stage renal death event and, separately, the death event, on a group of patients with chronic kidney disease grade 3-5 (Table IV). Lastly, the probability of death in patients undergoing dialysis was obtained from a study by De Nicola et al. in 2010 [44]. Table IV shows the transition probabilities used in the Markov model.

**Table II.** Breakdown of the probability of death and end-stage renal disease for patients with CKD.

	Conte et al. 2011	Percentage
Dialysis split	8.30%	58.5%
Death split	5.90%	41.5%
	<b>14.20%</b>	100.0%

Source: De Nicola et al. 2011 [44]

**Table III.** Transition probabilities used in the Markov model

Weighted probabilities for the LOW-PROTEIN DIET arm				
	Base case	Minimum	Maximum	Absolute values at 1 year
Low-protein diet → low-protein diet	90.05%	97.03%	50.00%	45,531
Low-protein diet → Haemodialysis	5.82%	1.74%	29.23%	2,941
Low-protein diet → Death	4.13%	1.24%	20.77%	2,090
Total death and ESRD	9.95%	2.97%	50.00%	5,031
Probability of death and DIALYSIS	10.00%	8.00%	12.00%	294
Weighted probabilities for the NO TREATMENT arm				
	Base case	Minimum	Maximum	Absolute values at 1 year
No treatment → No treatment	82.66%	93.84%	22.22%	41,796
No treatment → Haemodialysis	10.13%	3.60%	45.46%	5,124
No treatment → Death	7.20%	2.56%	32.32%	3,642
Total death and ESRD	17.34%	6.16%	77.78%	8,766
Probability of death and DIALYSIS	10.00%	8.00%	12.00%	512

Source: Foque and Laville (Cochrane) 2009 [26], De Nicola et al. 2011 [34], De Nicola et al. 2010 [44]

**Model utility estimate:** Since the methodology involves the use of cost utility analysis (CUA), it was necessary to estimate the utility values. The scores used were extrapolated from the study by Gorodetskaya et al. in 2005 <sup>[45]</sup>. In this study, the authors consider a cohort of 205 USA patients with a mean age of 62.8±12.7 years and a gender composition with 52% of female patients. Various estimates were obtained by administering various questionnaires, such as: Kidney Disease Quality of Life Short Form 36 (KDQOL-36TM), Health Utilities Index (HUI)-3 and Time-Trade-Off (TTO). In our model, we used utilities estimated using the Time-Trade-Off approach. In particular, the utilities of patients with CKD 4 or 5, corresponding to 115 subjects, were observed and calculated from two to eight times in the subsequent two years. Table V shows the scores considered.

**Table IV.** Utilities estimated using Time-Trade-Off. Gorodetskaya et al. 2005

Utility	Base Case	Min	Max
CKD4 = GFR 30-60	0.850	0.833	0.867
Haemodialysis	0.72	0.713	0.727

**Model cost estimate:** The costs of dialysis that we considered, were estimated by the study processed by Censis “Renal replacement therapy in Italy” in 2009 <sup>[46]</sup>. The estimate was performed on the basis of two main categories: medical direct costs (all the monetary costs generated directly by dialysis treatment) and non-medical direct costs (all those costs that make treatment possible but that are not directly generated by it). Indeed, the costs were estimated on the analysis of 400,000 procedures provided in 2007 by 14 centres in the four regions considered. The basic estimate for each item was conducted per unit cost of the dialysis procedure belonging to the “diet phase” only (costs associated with the therapy “start-up phase” were not considered). In our model, for dialysis procedure we only considered haemodialysis as this was the treatment provided in the vast majority of cases. On average, the medical direct cost of a haemodialysis session comes to €166.42, the non-medical direct costs to €51.39.

When these items are added together, each haemodialysis session has a cost of €217.81 and considering that a patient has three sessions a week, the cost per week of treatment is €653.43. Overall, the estimated annual cost per patient of haemodialysis comes to €34,072.

For the costs of the low-protein was assumed a public payer perspective, so the diet cost of the low-protein diet refer to the reimbursement paid in the Lazio region for patients with chronic kidney disease on a low-protein diet, pursuant to Regional Government Resolution no.103 of 19 February 2010, of €120 a month per person <sup>[47]</sup>. Considering the financial contribution provided and not the cost associated with treatment incurred by the individual patient, reference is made to the “real” direct cost incurred by the health service, in line with the study’s perspective. More specifically, the products for which reimbursement is paid are: bread, pasta, flour, rusks, sliced bread, biscuits and other low-protein products indicated on the diet. We consider this figure as inclusive of the costs of the specialist nephrology and dietology appointments attended by the patient.

**Economic and statistical analysis:** The cost results are indicated as the total sum of the costs attributed to each patient undergoing each of the different treatments (cost in €). The

effectiveness results are expressed in terms of QALY lived by patients in the model's lifecycle.

The comparison in terms of cost-effectiveness (the cost of one incremental unit of effectiveness) between the different treatment sequences is expressed as the Incremental Cost-Effectiveness Ratio (ICER). The ratio is the result of the differences in cost between the two treatment arms compared divided by the difference in effectiveness of the same treatments:

$$ICER = \frac{C_A - C_B}{E_A - E_B}$$

Using this ratio, we can observe the cost-effectiveness of the low-protein diet treatment compared to no treatment of CKD in non-dialysed patients.

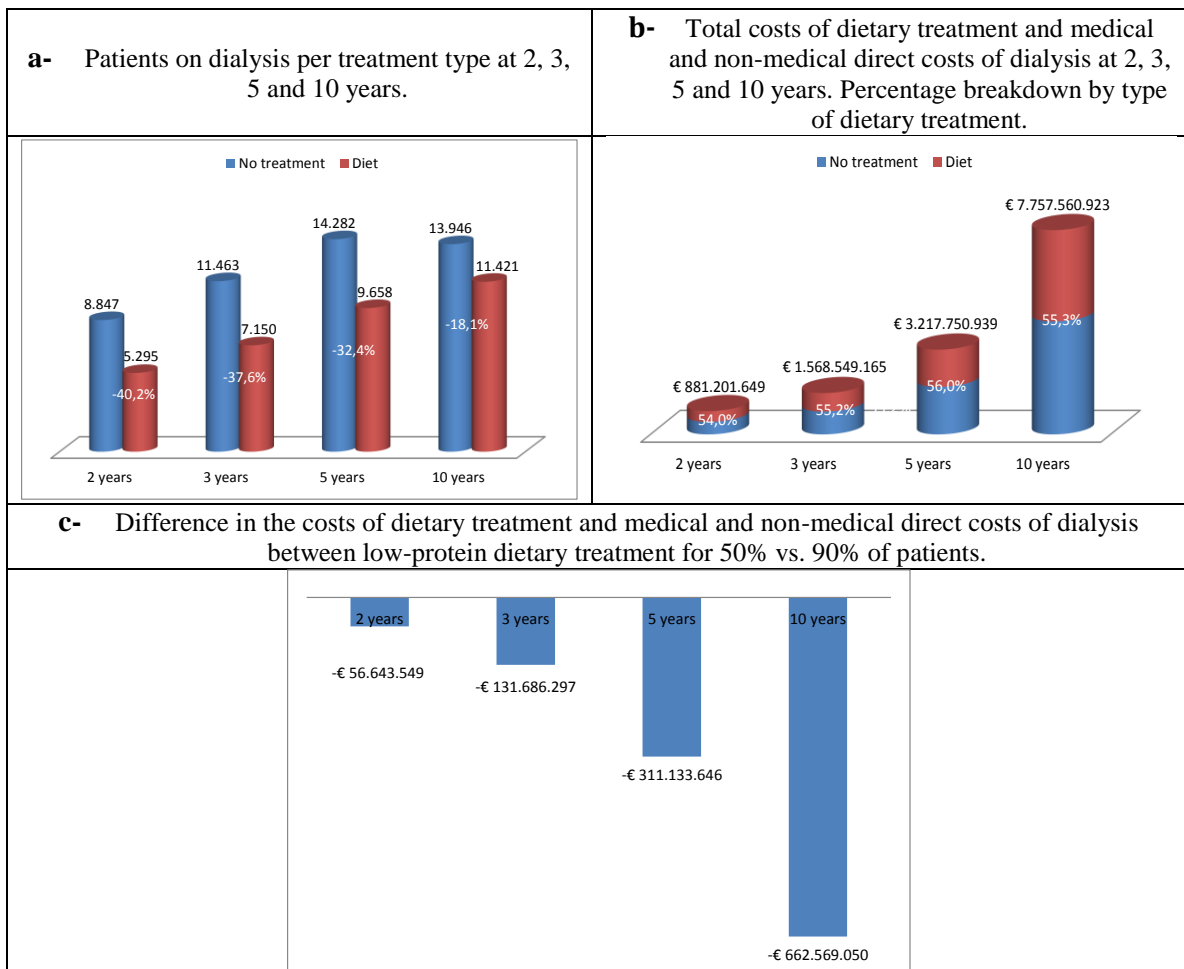
## **RESULTS:**

Cost and effectiveness results: By assuming an equal split between dietary treatment and no dietary treatment of prevalent patients in Italy today, Figure 2-a shows how many patients, according to our model, require dialysis treatment after 2, 3, 5 and 10 years for the two different arm. In all the ranges considered, we can always observe a fairly significant difference between the numbers of patients on dialysis for the two types of dietary treatment. The gap between the two groups of dialysed patients tends to close over time as the clinical programme is based on the assumption that, sooner or later, all patients with CKD require dialysis treatment, unless they die beforehand for other causes. Indeed we can observe a reduction in the gap from about 40% after two years of observation to approximately 18% after 10 years, corresponding, in absolute terms, to a difference of just over 3,500 patients after two years and approximately 2,500 patients after 10 years' treatment.

Figure 2-b shows the total costs (calculated as the sum of the total costs associated with dietary treatment, for the arm allocated this treatment and the medical and non-medical direct costs for haemodialysis treatment) in different time intervals, diversified for the two treatment arms. In total, the costs amount to approximately 880 million euros in the second year, before almost doubling in the third year (1.5 billion euros), reaching 3.2 billion at five years and 7.7 billion at the end of the tenth year. More specifically, in all the intervals considered, the arm of patients not receiving low-protein dietary treatment shows an increasing weight on total expenditure, increasing from 54% after two years to about 55% after ten years. In absolute terms, there is an increase in the difference in costs between the two arms of approximately 70 million euros in the second year to 828 million in the tenth year.

We then compared the total costs produced between the basic assumptions of treatment with a low-protein diet of 50% of CKD patients with the assumption that 90% of patients are treated with a low-protein diet (40% increase). The increasing number of dialysis sessions avoided thanks to treatment by low-protein diet entails increasingly significant savings over the years as shown in Figure 2-c. This means that subjecting a further 40% of patients to low-protein dietary treatment, would involve a saving that for each range more than doubles the savings obtained in the previous period. After two years, the savings amount to 56 million euros before more than doubling after three years' observation (131 million euros), they reach 311 million euros at the end of the first five years and, lastly, at the tenth year, we obtain savings of approximately 662 million Euros, almost 12 times the estimated savings for the second year.





**Figure 2 (a, b, c).** Cost and Effectiveness results.

**Cost-effectiveness results:** As was predicted, by examining the results of the cost-effectiveness analysis, treatment with a low-protein diet appears to be more efficacious in terms of years of good overall quality of life in all the time intervals considered. The difference in terms of QALY is always in favour of the dietary treatment, starting from 0.09 after the first two years, before doubling and quadruplicating after 3 (0.17) and 5 years (0.37), up to a difference of one year (1.02) lived healthy after the first 10 years of treatment (Table VII).

The same situation is also observed for average costs per patient: In all cases the treatment is in favor of the low-protein treatment and after two years the gap amounts to €1,400, before more than doubling (€3,256) and quadruplicating (€7,692) in the subsequent intervals to reach a gap of €16,380 after ten years.

In terms of cost-effectiveness, we find that the low-protein dietary treatment is always dominant in all the intervals considered and regardless of whether all the cost items are included in the calculation. Dominance is due to the fact that the treatment is more effective in terms of years of good quality of life gained and is, at the same time, less expensive.

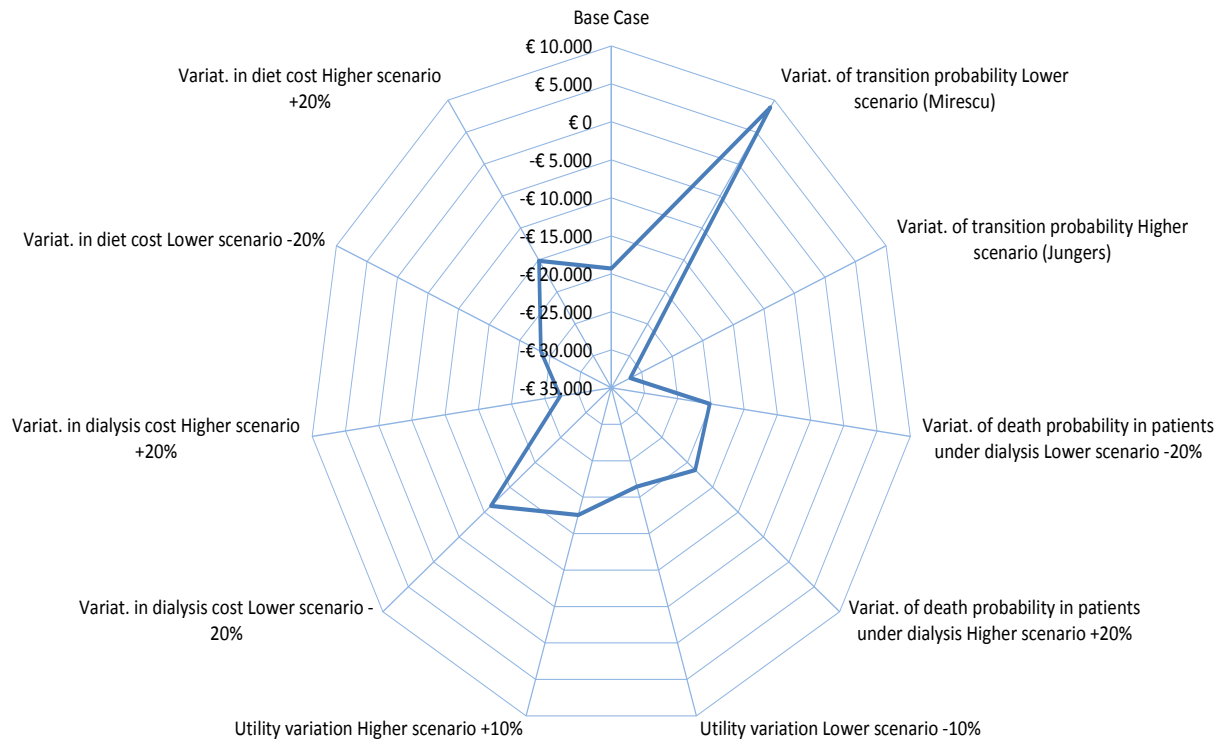
**Table V.** Cost-effectiveness analysis for low-protein diet vs. no dietary treatment. Mean values per patient at 2, 3, 5 and 10 years.

2 years					
	Cost	QALY	Incremental QALY	Incremental COST	ICER
No diet	€ 9,414	1.48			
diet	€ 8,014	1.57	0.09	-€ 1,400	DOMINANT
3 years					
	Cost	QALY	Incremental QALY	Incremental COST	ICER
No diet	€ 17,139	2.13			
diet	€ 13,883	2.29	0.17	-€ 3,256	DOMINANT
5 years					
	Cost	QALY	Incremental QALY	Incremental COST	ICER
No diet	€ 35,665	3.24			
diet	€ 27,974	3.62	0.37	-€ 7,692	DOMINANT
10 years					
	Cost	QALY	Incremental QALY	Incremental COST	ICER
No diet	€ 84,903	5.24			
diet	€ 68,523	6.26	1.02	-€ 16,380	DOMINANT

**Sensitivity analysis:** The Figure 3 shows the different ICER obtained from the variation of the individual parameters of the model. For each parameter was considered a lower scenario and an higher scenario. The deterministic sensitivity analysis (Figure 3) shows a substantial robustness of the model's results since the ICER value shows a dominance of the low protein diet after three years, in all the ten variations considered, except for one. In fact, by using the study transition probabilities, out of the seven being considered, with the lowest mortality and renal mortality values (Mirescu 2007)<sup>[38]</sup> for both arms of treatment (consequently with a greater probability to remain in a kidney failure condition), ICER reaches a value of about €8,800 for QALY gained (with a 45% increase versus the base case value of -€19,298), significantly below the threshold of €40,000. Conversely, by using the study transition probabilities with the highest mortality and renal mortality values (Jungers 1987)<sup>[40]</sup>, ICER is clearly dominant with a -€31,800 value (equal to a 65% decrease versus the base case value).

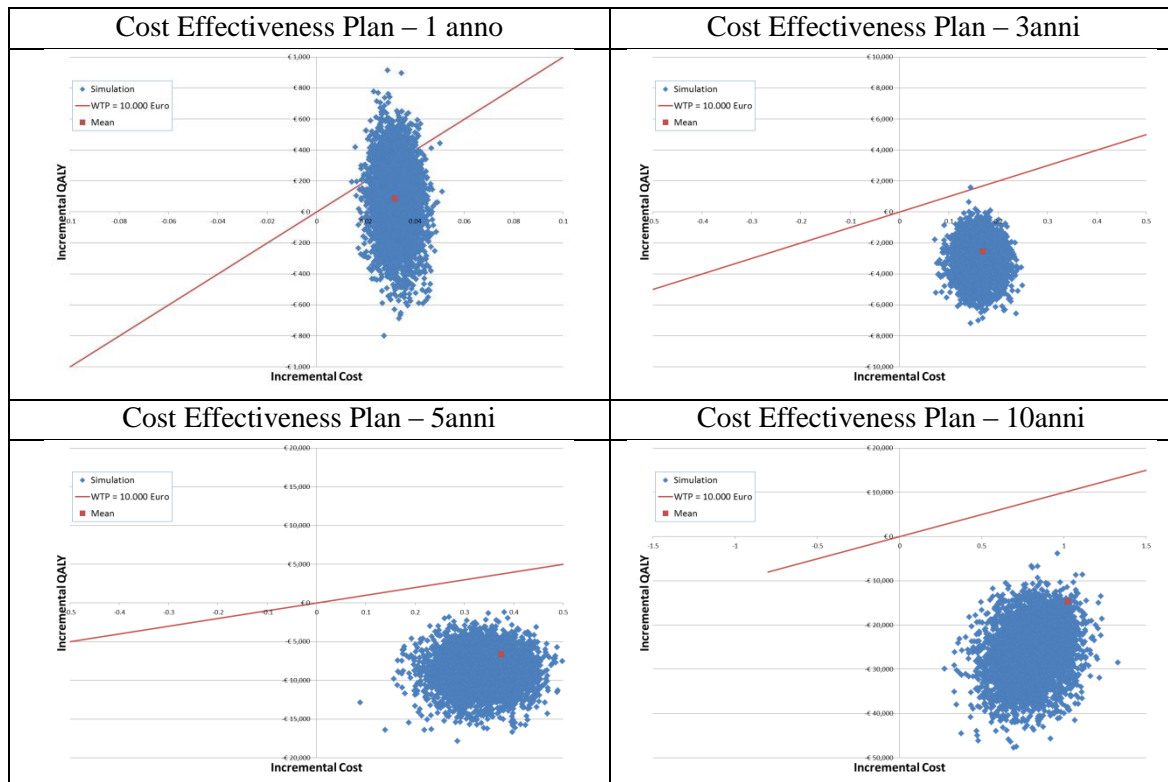
A significant ICER variation occurs when the dialysis costs change: with a 20% increase in costs, we see a decrease in ICER and by contrast, with a 20% decrease in costs, ICER is higher and in both cases it can be quantified as a variation of about 41% of the values obtained in the base case (with ICER equal to -€11,270 in the cost reduction scenario and -€27,326 in the cost increase scenario). A less substantial variation, but still significant, is observed in the costs of the diet. In contrast with the results of the dialysis cost analysis, a 20% increase in the treatment costs shows an increase of the ICER value by about 21% versus the base case value, whereas we see a 20% reduction of the ICER value when we reduce by 20% the costs of the low protein treatment.

The variations in the other parameters of the model ( $\pm 20\%$  probability of death in patients treated with dialysis, and patient utility associated with the different degrees of the disease  $\pm 10\%$ ) do not involve a significant variation of the ICER.



**Figure 3.** Radar Chart and Sensitivity analysis on the ICER value

The probabilistic sensitivity analysis confirms again the robustness of the model's results. Figure 4 shows that after one year, 82.8% of the simulations produce an ICER value below the willingness to pay of €10,000. After 3 years, 100% of the simulations determines an ICER value below € 10,000 and almost always dominant. After five and ten years, the low protein treatment continues to be dominant.



**Figure 4.** Probabilistic sensitivity analysis on the ICER value. Values at 1, 3, 5, 10 years

## **CONCLUSIONS:**

Chronic renal failure represents, therefore, a major issue for the NHS due to the high increase of its incidence and prevalence as well as for the high social costs associated with the management of the disease.

More specifically, and with a particular reference to medical and non-medical direct costs, an average annual cost per patient under dialysis was estimated to be about €34,071.70 (i.e. €653.43 per week). This figure, which is very important both in terms of quality of life and impact on costs, suggests the need to resort to alternative treatments which, although they may not solve the problem, can significantly delay the use of dialysis. The low protein diet, as reported in scientific literature, has demonstrated to be the best alternative in order to delay dialysis<sup>[24,25,26]</sup>.

But in terms of healthcare politics and planning, it is essential to demonstrate also an economic advantage (sustainability) deriving from the use of a low-protein diet.

A Cost-Utility analysis has demonstrated that the low protein diet treatment is dominant in all the intervals being studied and with all the cost items whether entered or not into the calculation. The dominance is due to the fact that the treatment has demonstrated to be more effective in terms of quality-adjusted life year gained (QALY) and, at the same time, less expensive because of low direct cost.

Furthermore, with a specific reference to the costs, the analysis has demonstrated how the growing number of avoided dialysis, thanks to the low-protein diet treatment, achieves a sizeable savings throughout the years (see Figure 2-c). Consequently, by having an increasingly higher number of patients undergoing a low-protein diet treatment, the savings could amount to €56 million beginning already in the second year, they could more than double after three years of observation (€131 million) and reach, by the tenth year, about €662 million, i.e. 12 times more the savings estimated for the second year.

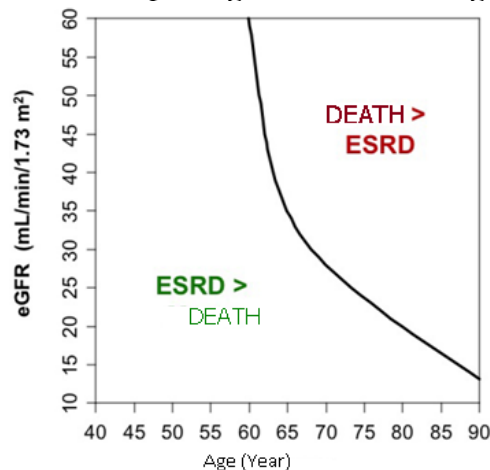
The results obtained can be considered conservative. In fact, in our analysis we have not taken into consideration the impact of indirect costs (which will be the subject matter of a second study) and we did not take into consideration a certain level of inappropriateness deriving from the fact that patients above 75 years of age are prescribed dialysis, although with less frequency.

This second aspect is particularly important not only in terms of efficacy and appropriateness of the intervention but also from a cost perspective.

In fact, some recent studies have analysed the effects of a conservative therapy, as an alternative to dialysis, for patients > 75 years of age with IRC<sup>[48, 49, 50]</sup>. Comparative studies have shown that there is no significant advantage, in terms of survival, for the patients who undergo dialysis versus the patients treated with a conservative therapy (low protein diet)<sup>[17, 18]</sup>, not even in terms of fewer hospitalisation days<sup>[51]</sup>.

More specifically, for most patients with ESRD, the dialysis guarantees an important survival rate. However, in those patients >75, this benefit is evident exclusively in patients without co-morbidity. Obviously, this does not mean the dialysis does not involve advantages for elderly patients with ESRD. The dialysis benefits elderly patients with very low co-morbidities and with a rapid decline of renal functions. By contrast, the same studies have shown how a conservative therapy (low protein diet) plays an important role in patients with co-morbidity (medium and high) and in patients characterised by a slow decline of renal functions.

Data in the scientific literature, in reference to patients > 75 years, suggests that the conservative treatment (low protein diet) can certainly represent, for this sub-population, a major advantage in terms of QoL together with a savings in resources for the NHS.



**Figure 3.** Risk of death per age group and GFR. Reviewed by <sup>[52]</sup>: O'Hare et al 2006<sup>[53]</sup>

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